**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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| In re application of: | Examiner: Kemmerer, Elizabeth |
| Avi ASHKENAZI, et al. | Art Unit: 1646 |
| Application Serial No. 09/941,992 | Confirmation No: 8312 |
| Filed: August 28, 2001 | Attorney's Docket No. 39780-2730 P1C1 |
| For: **SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME** | **Customer No. 35489** |

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## ON APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES

## APPELLANTS' BRIEF

**MAIL STOP APPEAL BRIEF - PATENTS**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

This Appeal Brief, filed in connection with the above captioned patent application, is responsive to the Final Office Action mailed on September 16, 2004. A Notice of Appeal was filed herein on January 12, 2005. A request for a five month extension of time is filed concurrently herewith. Appellants hereby appeal to the Board of Patent Appeals and Interferences from the final rejection in this case.

The Commissioner is authorized to charge any fees which may be required, including extension fees, or credit any overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2730 P1C1**.

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The following constitutes the Appellants' Brief on Appeal.

## I. REAL PARTY IN INTEREST

The real party in interest is Genentech, Inc., South San Francisco, California, by an assignment of the parent application, U.S. Serial No. 09/941,992 recorded November 16, 2001, at Reel 012176 and Frame 0450.

## II. RELATED APPEALS AND INTERFERENCES

The claims pending in the current application are directed to a polypeptide referred to herein as "PRO341". There exist two related patent applications, (1) U.S. Serial No. 09/990,711, filed November 14, 2001 (containing claims directed to antibodies to the PRO341 polypeptide), and (2) U.S. Serial No. 09/991,150, filed November 16, 2001 (containing claims directed to nucleic acids encoding PRO341 polypeptides). These two related applications are also under final rejection from the same Examiner and based upon the same outstanding rejection, therefore appeal of these final rejections are being pursued independently and concurrently herewith.

## III. STATUS OF CLAIMS

The current application was filed with Claims 1-118. In a Preliminary Amendment filed on January 7, 2002, Appellants canceled Claims 1-118 and added new claims 119-131. In an Amendment filed on October 27, 2003, Claims 119-123 and 128 were canceled and Claim 124 was amended. A Request for Continued Examination was filed July 7, 2004 in response to a Final Office Action dated January 21, 2004 wherein Claim 127 was canceled and Claims 124 - 126 were further amended. A second final rejection was mailed September 16, 2004 and a Notice of Appeal was filed on January 12, 2005. Claims 124-126 and 129-131 remain pending and under final rejection, wherein the final rejection of these claims is being appealed herein.

A copy of the rejected claims in the present Appeal is provided as Appendix A.

## IV. STATUS OF AMENDMENTS

In an Amendment filed on January 27, 2005 after the mailing of the Final Office of September 16, 2004, a request under Rule C.F.R. §1.48 for correction of inventorship was filed, but this amendment has not been entered for purposes of this appeal.

## V. SUMMARY OF INVENTION

Independent Claim 124 is directed to an isolated polypeptide comprising the amino acid sequence of a polypeptide referred to in the present application as "PRO341." PRO341 is a cell surface polypeptide, which is described as a novel polypeptide having a signal peptide sequence extending from about amino acid position 1 to about amino acid position 17 in the sequence of SEQ ID NO: 20 and seven transmembrane domains (see page 49, lines 3-8, and for example, Example 8 and Figure 12). The encoding PRO341 is shown for the first time in the present patent application to be (i) significantly overexpressed (or "upregulated") in human lung cell carcinomas as compared to normal, non-cancerous human tissue controls (Example 170). This feature is specifically recited in claim 124, and carried by all claims dependent from claim 124.

In particular, the amino acid sequence of the native "PRO341" polypeptide and the nucleic acid sequence encoding this polypeptide (referred to in the present application as "DNA26288-1239") are shown in the present specification as SEQ ID NOs: 20 and 19, respectively, and in Figures 12 and 11, respectively. Page 288, lines 14-17 of the specification provides the description for Figures 12 and 11. The cDNA for PRO341 was deposited under ATCC accession number 209792. Pending Claims 125-126 and 129-131 depend from Claim 124.

A PRO polypeptide sequence lacking the signal peptide (claim 124, part (b)) is described in the specification at, for example, page 305, lines 12-22, and page 49, lines 2-3. The preparation of chimeric PRO polypeptides (claims 130 and 131), including those wherein the heterologous polypeptide is an epitope tag or an Fc region of an immunoglobulin, is set forth in the specification at page 374, lines 24 to page 375, line 9. Examples 140-143 and page 376, line 12 onwards describe the expression of PRO polypeptides in various host cells, including *E. coli*, mammalian cells, yeast and Baculovirus-infected insect cells.

Finally, Example 170, in the specification at page 539, line 19, to page 555, line 5, sets forth a 'Gene Amplification assay' which shows that the PRO341 gene is amplified in the genome of certain human lung cancers (see Table 9A, page 550, third column). The profiles of various primary lung tumors used for screening the PRO polypeptide compounds of the invention in the gene amplification assay are summarized on Table 8, page 546 of the specification.

## VI. ISSUES BEFORE THE BOARD

1. Whether Claims 124-126 and 129-131 satisfy the utility requirement under 35 U.S.C. §101.

2. Whether Claims 124-126 and 129-131 satisfy the enablement requirement under 35 U.S.C. §112, first paragraph.

## VII. GROUPING OF CLAIMS

For the purposes of this appeal, all claims (Claims 124-126 and 129-131) stand and fall together.

## VIII. ARGUMENTS

***Summary of the Arguments***

Issue 1: Utility

Claims 124-126 and 129-131 stand rejected under 35 U.S.C. §101 as allegedly lacking either a specific and substantial asserted utility or a well established utility. Appellants have previously submitted that patentable utility of the PRO341 polypeptides is based upon the gene amplification data for the gene encoding the PRO341 polypeptide. The specification discloses that the gene encoding PRO341 showed significant amplification, ranging from 2.173 to 2.514 fold in three different lung primary tumors. Appellants have also submitted, with their Response filed October 24, 2003, the Declaration of Dr. Audrey Goddard, which explains that a gene identified as being amplified at least 2-fold by the disclosed gene amplification assay in a tumor sample relative to a normal sample is useful as a marker for the diagnosis of cancer, for monitoring cancer development and/or for measuring the efficacy of cancer therapy. Therefore, one of ordinary skill would find it credible that the claimed PRO341 polypeptides have utility as markers for the diagnosis of lung tumors.

However, the Examiner asserted on page 3 of the Final Office Action mailed September 16, 2004 that amplification of the PRO341 polynucleotide does not impart a specific, substantial, and credible utility to the PRO341 polypeptide since, "the literature reports that gene amplification does not *necessarily* result in increased expression at the mRNA and polypeptide

levels" (emphasis added). In support of this assertion, the Examiner cited references by Pennica *et al.* and Konopka *et al.*

Appellants submit that, the combined teachings of Pennica *et al.* and Konopka *et al.* are not directed towards genes in general but to a single gene or genes within a single family and thus, their teachings cannot support a general conclusion regarding correlation between gene amplification and mRNA or protein levels. Therefore, a prima facie case for lack of utility has not been established.

In contrast, Appellants have submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. First, the articles by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* (made of record in Appellants' Response filed July 7, 2004) collectively teach that in general, gene amplification increases mRNA expression. Second, the Declaration of Dr. Paul Polakis (made of record in Appellants' Response filed July 7, 2004), principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application, shows that, in general, there is a correlation between mRNA levels and polypeptide levels . Appellants further note that the sale of gene expression chips to measure mRNA levels is a highly successful business, with a company such as Affymetrix recording 168.3 million dollars in sales of their GeneChip arrays in 2004. Clearly, the research community believes that the information obtained from these chips is useful (i.e., that it is more likely than not informative of the protein level).

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is a correlation between DNA, mRNA, and polypeptide levels, these instances are exceptions rather than the rule. In the majority of amplified genes, as exemplified by Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, and the Polakis Declaration, the teachings in the art overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO341 gene, that the PRO341 polypeptide is concomitantly overexpressed. Thus, the claimed PRO341 polypeptides have utility in the diagnosis of cancer.

Appellants further submit that even if there is no correlation between gene amplification and increased mRNA/protein expression, (which Appellants expressly do not concede), a polypeptide encoded by a gene that is amplified in cancer would still have a specific, substantial,

and credible utility. Appellants submit that, as evidenced by the Ashkenazi Declaration (made of record in Appellants' Response filed October 24, 2003) and the teachings of Hanna and Mornin (made of record in Appellants' Response filed July 7, 2004), simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy for the tumor, as demonstrated by the real-world example of the breast cancer marker HER-2/neu.

Accordingly, Appellants submit that when the proper legal standard is applied, one should reach the conclusion that the present application discloses at least one patentable utility for the claimed PRO341 polypeptides.

Issue 2: Enablement

Claims 124-126 and 129-131 stand rejected under 35 U.S.C. §112, first paragraph, allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention." (Page 3 of the Final Office Action mailed September 16, 2004).

Appellants submit that, as discussed above, the PRO341 polypeptides have utility in the diagnosis of cancer. Based on such a utility, one of skill in the art would know exactly how to use the claimed polypeptides for diagnosis of cancer, without any undue experimentation. The specification provides ample guidance to allow the skilled artisan to identify those polypeptides which meet the limitations of the claims, including a detailed protocol for the gene amplification assay, and detailed guidance as to how to identify and make polypeptides of PRO341 (SEQ ID NO:20). Accordingly, one of ordinary skill in the art would understand how to make and use the recited polypeptide variants without any undue experimentation.

***Response to Rejections***

Issue 1. Claims 124-126 and 129-131 are supported by a credible, specific and substantial asserted utility, and thus meet the utility requirement of 35 U.S.C. § 101

The sole basis for the Examiner's rejection of claim 124-126 and 129-131 under this section is that the data presented in Example 170 of the present specification is allegedly

insufficient under the present legal standards to establish a patentable utility under 35 U.S.C. § 101 for the presently claimed subject matter. Appellants strongly disagree and, therefore, respectfully traverse the rejection.

A. The Legal Standard For Utility Under 35 U.S.C. § 101

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001), an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility".

Under the Utility Guidelines, an asserted utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a particular composition of matter is useful in general as a diagnostic tool, without also identifying the particular condition that is to be diagnosed using that diagnostic tool. However, when the condition that is capable of being diagnosed is specifically identified and linked to the claimed subject matter, the asserted utility satisfies the "specificity" requirement.

The requirement of a "substantial" utility defines a "real world" use, and derives from the U.S. Supreme Court's holding in Brenner v. Manson, 383 U.S. 519, 534 (1966) stating that:

> "[t]he basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility."

In explaining the "substantial" utility standard, the Manual of Patent Examining Procedure (MPEP) § 2107.01 cautions, however, that Patent Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient" (MPEP § 2107.01, emphasis supplied). Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in MPEP § 2107 II(B)(1) gives the following instruction to patent examiners:

> "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility". (Emphasis supplied).

Moreover, the Utility Guidelines make clear that the requirement for the asserted utility be "substantial" arises solely for the purpose of excluding:

> "'throw-away' or 'insubstantial'.....utilities, such as the use of a complex invention as landfill, as a way of satisfying the utility requirement of 35 U.S.C. § 101". (66 Fed. Reg. 1092, 1098 (2001), emphasis supplied).

Finally, the Utility Guidelines also restate the Patent Office's long established position that any asserted utility must be "credible". "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the applicant's assertions." (MPEP § 2107 II(B)(1)(ii)). According to the Revised Interim Utility Guidelines Training Materials published by the U.S. Patent Office in 1999, Office personnel must always accept a patent applicant's assertion of utility as "credible" unless (1) the logic underlying the assertion is "seriously flawed", or (ii) if the facts upon which the assertion of utility is based are "inconsistent with the logic underlying the assertion".

Moreover, the U.S. Patent Office also sets forth the evidentiary standard as to utility rejections under 35 U.S.C. § 101. In general, an Applicant's assertion of utility creates a presumption of utility that is sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." In re Langer, 503 F.2d 1380, 1391 (CCPA 1974). See, also In re Jolles, 628 F.2d 1322 (CCPA 1980); In re Irons, 340 F.2d 974 (CCPA 1965); In re Sichert, 566 F.2d 1154, 1159 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a question of fact. Raytheon v. Roper, 724 F.2d 951, 956 (Fed. Cir. 1983) cert. denied, 469 U.S. 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. In re Oetiker, 977 F.2d 1443, 1445 (Fed. Cir. 1992). Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Absolute predictability is not a requirement. Only after the Examiner makes a proper *prima facie* showing under this standard does the burden of rebuttal shift to the patent applicant.

B. The Data and Documentary Evidence Supporting a Patentable Utility

The data presented by the Appellants in the present application and which underlies the current dispute is presented in Example 170 starting on page 539 of the specification. Example 170 describes the results obtained using a very well-known and routinely employed polymerase chain reaction (PCR)-based assay, the TaqMan™ PCR assay, also referred to herein as the gene amplification assay. This assay allows one to quantitatively measure the level of gene amplification in a given sample, say, a tumor extract, or a cell line. It was well known in the art at the time the invention was made that gene amplification is an essential mechanism for oncogene activation. Appellants isolated genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 9A (pages 539 onwards of the specification), including primary lung cancers of the type and stage indicated in Table 8 (page 546). The tumor samples were tested in triplicates with Taqman™ primers and with internal controls, beta-actin and GADPH in order to quantitatively compare DNA levels between samples (page 548, lines 33-34). As a negative control, DNA was isolated from the cells of ten normal healthy individuals, which was pooled and used as a control (page 539, lines 27-29) and also, no-template controls (page 548, lines 33-34). The results of TaqMan™ PCR are reported in ΔCt units, as explained in the passage on page 539, lines 37-39. One unit corresponds to one PCR cycle or approximately a 2-fold amplification, relative to control, two units correspond to 4-fold, 3 units to 8-fold amplification and so on . Using this PCR-based assay, Appellants showed that the gene encoding for PRO341 was significantly amplified, that is, it showed approximately 1.12-1.33 ΔCt units which corresponds to $2^{1.12}$ -$2^{1.33}$- fold amplification or 2.173 fold to 2.514-fold amplification in three lung tumors.

In support of their showing that these gene amplification values are significant, Appellants submitted, in their Response filed October 24, 2003, a Declaration by Dr. Audrey Goddard. Appellants particularly draw the Board's attention to page 3 of the Goddard Declaration which clearly states that:

> It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.*, non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a

> gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy. (Emphasis added).

Accordingly, the 2.173-fold to 2.514-fold amplification observed for PRO341 in the three lung tumors would be considered significant and credible by one skilled in the art, based upon the facts disclosed in the Goddard Declaration.

It is also well known that gene amplification occurs in most solid tumors, which includes lung carcinomas, and is generally associated with poor prognosis. Therefore, the PRO341 gene becomes an important diagnostic marker to identify such malignant lung carcinomas, even when the lung malignancy associated with PRO341 molecule is a rare occurrence. Accordingly, the present specification clearly discloses enough evidence that the gene encoding the PRO341 polypeptide is significantly amplified in certain types of lung carcinoma tumors and is therefore, a valuable diagnostic marker for identifying certain types of lung carcinomas.

In addition, Example 170 in the specification further discloses, "Amplification is associated with overexpression of the gene product, indicating that the polypeptides are useful targets for therapeutic intervention in certain cancers such as colon, lung, breast and other cancers and diagnostic determination of the presence of those cancers" (emphasis added). Besides, Appellants have submitted ample evidence (discussed below) to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level as well.

First, the articles by Ornfoft *et al.*, Hyman *et al.*, and Pollack *et al.* (made of record in Appellants' Response filed July 7, 2004) collectively teach that in general, for most genes, DNA amplification increases mRNA expression. The results presented by Ornfoft *et al.*, Hyman *et al.*, and Pollack *et al.* are based upon wide ranging analyses of a large number of tumor associated genes. Ornfoft *et al.* studied transcript levels of 5600 genes in malignant bladder cancers, many of which were linked to the gain or loss of chromosomal material, and found that in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts. Hyman *et al.* compared DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, and found that there was evidence of a prominent global influence of copy number changes on gene expression levels. In

Pollack *et al.*, the authors profiled DNA copy number alteration across 6,691 mapped human genes in 44 predominantly advanced primary breast tumors and 10 breast cancer cell lines, and found that on average, a 2-fold change in DNA copy number was associated with a corresponding 1.5-fold change in mRNA levels. In summary, the evidence supports the Appellants' position that gene amplification is more likely than not predictive of increased mRNA and polypeptide levels.

Second, the Declaration of Dr. Paul Polakis (made of record in Appellants' Response filed July 7, 2004), principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application, explains that in the course of Dr. Polakis' research using microarray analysis, he and his co-workers identified approximately 200 gene transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Subsequently, antibodies binding to about 30 of these tumor antigens were prepared, and mRNA and protein levels were compared. In approximately 80% of the cases, the researchers found that increases in the level of a particular mRNA correlated with changes in the level of protein expressed from that mRNA when human tumor cells are compared with their corresponding normal cells. Therefore, Dr. Polakis' research, which is referenced in his Declaration, shows that, in general, there is a correlation between increased mRNA and polypeptide levels.

Taken together, all of the submitted evidence supports the Appellants' position that, increased gene amplification levels, more likely than not, predict increased mRNA and polypeptide levels, which clearly meets the utility standards described above. Hence, one of skill in the art would reasonably expect that, based on the gene amplification data of the PRO341 gene, the PRO341 polypeptide is concomitantly overexpressed in the lung tumors studied as well.

Appellants further submit that, even if there were no correlation between gene amplification and increased mRNA/protein expression, (which Appellants expressly do not concede), a polypeptide encoded by an amplified gene in cancer would **still** have a specific, substantial, and credible utility as explained below. As the Declaration of Dr. Avi Ashkenazi (submitted with Appellants' Response filed October 24, 2003) explains:

> "even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment."

Additional supporting evidence for such a utility is presented in a real-world example in an article by Hanna and Mornin (submitted with Appellants' Response filed July 7, 2004), which demonstrates a use for the breast cancer marker HER-2/neu. Hanna and Mornin teach that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH), as well as, the over-expression of the HER-2/neu gene product (by IHC). Even when the protein is not over-expressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it. Thus, as evidenced by the Ashkenazi Declaration and the teachings of Hanna and Mornin, one skilled in the art would appreciate that simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, were not over-expressed. This leads to better determination of a suitable therapy for the tumor. Such testing is for the purpose of characterizing not the PRO341 polypeptide, but the tumors in which the gene encoding PRO341 is amplified. Therefore, the PRO341 polypeptide is also useful in tumor categorization, the results of which become an important tool in the hands of a physician enabling the selection of a treatment modality that holds the most promise for the successful treatment of a patient.

Based on the gene amplification data presented for PRO341 in Example 170 of the specification, and all the submitted evidence, there is ample support for the Appellants' position that increased gene amplification levels, more likely than not, predict increased mRNA and polypeptide levels. One of skill in the art would therefore reasonably expect, based on: (a) the gene amplification data for the PRO341 gene, (b) the supportive evidence in the Declarations submitted, and, (c) the supportive articles presented by the Appellants which were available in the art at the time of filing of the instant application, that the PRO341 polypeptide is most likely to be concomitantly, overexpressed in certain lung tumors, just like the PRO341 gene, and is therefore useful as a tumor marker for these types of lung cancers. Even in the event that the PRO341 polypeptide were found not to be overexpressed in the lung tumors where the PRO341 gene were amplified, (a position expressly not conceded to), the PRO341 polypeptide is still

useful as a marker in tumor categorization and becomes an useful tool, enabling the physician to decipher appropriate lines of treatment for the cancer patient, which is a real-life utility.

Contrary to the Appellants assertion of utility, however, the Examiner alleges that the gene amplification results presented in Example 170 does not render the presently claimed polypeptides patentably useful, and, finds the declaratory evidence presented in this case, for what Appellants consider legally inappropriate reasons, "non-persuasive". Appellants respectfully submit, however, that upon application of the proper legal standards described above, the appropriate conclusion is that the present application does, in fact, disclose at least one patentable utility for the claimed PRO341 polypeptide.

C. Proper Legal Analysis of the Data and Documentary Evidence

Appellants respectfully submit that the data presented in Example 170 of the specification and the cumulative evidence of record support a "specific, substantial and credible" asserted utility for the presently claimed invention.

(i) and (ii) The Requirements For "Specific" and "Credible" Utility

The requirements as set forth in the above described Utility Guidelines under 35 U.S.C. § 101 is that an asserted utility for a claimed invention must be "specific" and "credible".

Appellants have clearly demonstrated that the nucleic acid encoding the PRO341 polypeptide of SEQ ID NO: 20 is detectably amplified in certain cancerous human lung tumors and correspondingly, it is more likely than not that the PRO341 polypeptide is also overexpressed in certain lung tumors. Even if the PRO341 polypeptide is not overexpressed while the PRO341 gene levels are amplified in a given lung tumor, this information is still useful in lung tumor categorization. As such, one of ordinary skill in the art can readily see that the presently claimed PRO341 polypeptides would be quite useful as a diagnostic tool for further classifying human lung carcinomas of unknown pathology. Such a use, in turn, provides valuable therapeutic information for determining the modes of treating the cancer patient.

In this regard, on page 3 of the Office Action of the Final Office Action mailed on September 16, 2004, the Examiner says :

"the rejection does not question the presumption of truth, or credibility of the asserted utility. The asserted utilities of cancer diagnostics and cancer therapeutics for the claimed polypeptides (sic., "antibodies") are credible and specific" (emphasis added).

Therefore, Appellants respectfully submit, and the Examiner agrees, that the present invention clearly satisfies the "specificity" and "credible" requirement.

(iii) The Requirement For A "Substantial" Utility

As described above, a third requirement set forth in the Utility Guidelines is that an asserted utility for a claimed invention must be "substantial", meaning that the claimed invention must serve a "practical purpose" (see MPEP § 2107 II(B)(1)) which is not a "throw-away or insubstantial [use], such as the use of a complex invention as landfill. (66 Fed. Reg. 1092, 1098 (2001), emphasis supplied).

a) *Appellants have provided a "reasonable use" for the invention which is sufficient to satisfy the requirements of "substantial utility"*

Appellants note that on page 3 of the Final Office Action mailed on September 16, 2004, the Examiner states:

"... (the asserted utilities) are not substantial. The data set forth in the specification are preliminary at best..... an asserted utility must exist in currently available form." (emphasis added).

First of all, MPEP § 2107.01 cautions the Patent Office personnel to be careful not to interpret the phrase "immediate benefit to the public" or similar formulations, used in certain court decisions, to mean that, products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. In this instance, the Examiner has done just that and interpreted the "substantial utility" requirement to mean that "an asserted utility must exist in currently available form," which is legally incorrect. In fact, MPEP § 2107.01 adds that, "(r)ather, **any reasonable use** that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient" (emphasis supplied). Appellants have clearly demonstrated at least one "reasonable use" for the PRO341 polypeptide, that is, as a diagnostic marker for detecting or at least classifying lung carcinomas. Such uses of the claimed invention serve a "practical purpose", which is not a

"throw-away or insubstantial [use], such as the use of a complex invention as landfill." That is, Appellants have for the first time identified a particular human gene, the PRO341 gene, that is differentially amplified in certain types of cancerous human lung tumors and this discovery provides for the first time, the ability to exploit this previously unknown, differential gene amplification pattern for the purpose of diagnosing or classifying lung tumors of previously unknown pathology, which is not a "throw-away or insubstantial [use]."

Besides, the data disclosed in the instant specification are not preliminary. As will be discussed in greater detail below, based on the gene amplification data presented for the PRO341 gene in Example 170 of the specification, and the available art, there is ample support for the Appellants' position that increased gene amplification levels, more likely than not, predict increased mRNA and polypeptide levels. Thus, by providing a "reasonable use" for PRO341, Appellants respectfully submit that they have satisfied the "substantial utility" requirement for utility.

b) *Appellants maintain that a prima facie case of lack of utility has not been established*

Appellants note that the Examiner points out throughout the Office Action, and especially on page 3 of the Final Office Action mailed on September 16, 2004, that:

> "The specification indicates that the PRO341 gene is amplified in certain cancers. However, the literature reports that gene amplification does not *necessarily* result in increased expression at the mRNA and polypeptide levels. See Pennica *et al.*, Konopka *et al.*, Haynes *et al.*, cited in the previous Office Action." (emphasis added).

Appellants strongly disagree. Appellants submit that the Examiner applied an improper legal standard when making this rejection. The evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant.

Accordingly, it is not a legal requirement to establish a necessary correlation between an increase in the copy number of the DNA and protein expression levels that would correlate to the

disease state or that it is imperative to find evidence that DNA amplification is "necessarily" or "always" associated with overexpression of the gene product. Appellants respectfully submit that when the proper evidentiary standard is applied, a correlation must be acknowledged.

Based on the two cited references, Pennica *et al.* and Konopka *et al.*, the Examiner concludes that:

> "the literature evidences that gene amplification does not *reliably* correlate with increased mRNA or polypeptide expression."

First of all, the teachings of Pennica *et al.* are specific to *WISP* genes, a specific class of closely related molecules. Pennica *et al.* showed that there was good correlation between DNA and mRNA expression levels for the *WISP-1* gene but not for *WISP-2 and WISP-3* genes.

But, the fact that in the case of closely related molecules, there seemed to be no correlation between gene amplification and the level of mRNA/protein expression does not establish that it is more likely than not, in general, that such correlation does not exist. As discussed above, the standard is not absolute certainty. Pennica *et al.* has no teaching whatsoever about the correlation of gene amplification and protein expression for genes in general.

Further, contrary to the Examiner's allegation in the Final rejection on page 4, lines 11-12, Appellants do not argue that the WISP-2 (or *abl*) gene(s) may be discrepancies. The Examiner has misinterpreted the Appellants statement(s) submitted in the response of October 24, 2003 (page 9, last line). Appellants quote verbatim what was submitted in their previous response:

> "The Examiner has not shown whether the lack or correlation observed for the family of WISP polypeptides is typical, or is merely a discrepancy, an exception to the rule of correlation."

What the Appellants submitted was that, through Pennica's teachings, the Examiner has not shown that the lack or correlation observed for the family of WISP polypeptides is typical of most genes. Indeed, the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level. In fact, as noted even in Pennica *et al.*, "[a]n analysis of *WISP*-1 gene amplification and expression in human colon tumors *showed a correlation between DNA amplification and over-expression* . . . "

(Pennica *et al.*, page 14722, left column, first full paragraph, emphasis added). Accordingly, Appellants respectfully submit that Pennica *et al.* teaches nothing conclusive regarding the absence of correlation between gene amplification and over-expression of mRNA or polypeptides in most genes, in general.

Similarly, in Konopka *et al.*, Appellants submit that the Examiner has generalized a very specific result disclosed by Konopka *et al.* to cover all genes. Konopka *et al.* actually state that "[p]rotein expression is not related to amplification of the ***abl*** gene but to variation in the level of *bcr-abl* mRNA produced from a single $Ph^1$ template." (See Konopka *et al.*, Abstract, emphasis added). The paper does not teach anything whatsoever about the correlation of protein expression and gene amplification in general, and provides no basis for the generalization that apparently underlies the present rejection. The statement of Konopka *et al.* that "[p]rotein expression is not related to amplification of the *abl* gene . . . " is not sufficient to establish a *prima facie* case of lack of utility.

In conclusion, to establish a *prima facie* case of lack of utility, it is not enough to show that for one particular gene, a correlation does not exist. Rather, the law requires that the Examiner has to show evidence that it is more likely than not that such correlation, in general, does not exist. Such a showing has not been made, therefore, the Examiner has not made a sufficient case for a *prima facie* case of lack of utility and therefore, the Patent Office has failed to meet its initial burden of proof that Appellants' claims of utility are not substantial.

Actually, one of the cited references, Haynes *et al.*, showed that "there was a general trend, although no strong correlation between protein [expression] and transcript levels." (see Figure 1 and page 1863, paragraph 2.1, last line). When the proper legal standard is used, this clearly supports Appellants' position. This is all that's needed to meet the "more likely than not" evidentiary standard. Again, *accurate prediction* is not the standard.

An additional point made by the Examiner in the Final Office action, at least on page 6, lines 1-2 and lines 14-17 is that:

> "the specification provides data showing a very small increase in DNA copy number, approximately 2-fold, in a few tumor samples for PRO341.....it was imperative to find evidence in the relevant scientific literature whether or not a small increase in DNA copy number would be considered by the skilled artisan to be predictive of increased mRNA and polypeptide levels.....Given how small the DNA copy number of PRO341 increased, and the evidence provided by Haynes *et al.*, Pennica *et al.*, and Konopka *et al.*,

it was clear that one skilled in the art would not assume that a small increase in gene copy number would correlate with significantly increased mRNA or polypeptide levels." (emphasis added).

Appellants strongly disagree. The Examiner seems to be applying a heightened utility standard in this instance, which is legally incorrect. Appellants showed that the gene encoding for PRO341 was significantly amplified 2.173 fold to 2.514-fold, in three lung tumors. These values are considered significant based on the Declaration by Dr. Audrey Goddard discussed above. By referring to the 2.173-fold to 2.514-fold amplification as "very small," the Examiner appears to ignore the teachings within an expert's declaration without any basis, or without presenting any evidence to the contrary. Appellants respectfully draw the Examiner's attention to the Utility Examination Guidelines (Part IIB, 66 Fed. Reg. 1098 (2001)) which states that:

> "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered".

Thus, barring evidence to the contrary, Appellants maintain that the fold amplification disclosed for the PRO341 gene is significant and forms the basis for the utility claimed herein.

Further, the Examiner seems concerned that data is provided "in a few tumor samples for PRO341". Appellants emphasize that they have shown significant DNA amplification in three out of the fourteen (3/14) lung tumor samples in Table 9A, Example 170 of the instant specification. The fact that 3/14 lung tumors tested positive in this study does not make the gene amplification data, by any means, less significant or spurious. As any skilled artisan in the field of oncology would easily appreciate, not all tumor markers are generally associated with every tumor, or even, with most tumors. In fact, some tumor markers are useful for identifying rare malignancies. That is, the association of the tumor marker with a particular type of tumor lesion may be rare, or, the occurrence of that particular kind of tumor lesion itself may be rare. In either event, even these rare tumor markers which do not give a positive hit for most common tumors, have great value in tumor diagnosis, and consequently, in tumor prognosis. The skilled artisan would certainly know that such tumor markers are very useful for better classification of tumors. Therefore, whether the PRO341 gene is amplified in three lung tumors or in most lung tumors is not relevant to its identification as a tumor marker, or its patentable utility. Rather,

whether the amplification data for PRO341 is considered significant is what lends support to its usefulness as a tumor marker.

Thus, the Examiner has not established a *prima facie* case for lack of utility. Rather, based on the significant gene amplification data observed for PRO341 in three lung tumors, Appellants submit that PRO341 has patentable utility as a lung carcinoma tumor marker and further submit that this part of the utility rejection is improper.

c) *It is "more likely than not" for amplified genes to have increased mRNA and protein levels*

Appellants have submitted ample, scientific literature evidence (submitted with Appellants' Response filed July 7, 2004) to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level.

First, the articles by Ornoft *et al.*, Hyman *et al.*, and Pollack *et al.*, (made of record in Appellants' Response filed July 7, 2004) collectively teach that in general, gene amplification increases mRNA expression. Appellants submit that these and numerous other articles show that generally, if a gene is amplified in cancer, it is more likely than not that the mRNA transcript will be expressed at an elevated level. For example, Ornoft *et al.* studied transcript levels of 5600 genes in malignant bladder cancers, many of which were linked to the gain or loss of chromosomal material using an array-based method. Ornoft *et al.* showed that there was a gene dosage effect and taught that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts" (see column 1, abstract). In addition, Hyman *et al.* showed, using CGH analysis and cDNA microarrays which compared DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, that there was "evidence of a prominent global influence of copy number changes on gene expression levels." (See page 6244, column 1, last paragraph). Additional supportive teachings were also provided by Pollack *et al.*, who studied a series of primary human breast tumors and showed that "...62% of highly amplified genes show moderately or highly elevated expression, and DNA copy number influences gene expression across a wide range of DNA copy number alterations (deletion, low-, mid- and high-level amplification), and that on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold

change in mRNA levels." Thus, these articles collectively teach that in general, gene amplification increases mRNA expression.

In addition, in their Response filed July 7, 2004, Appellants submitted a Declaration by Dr. Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application, to show that mRNA expression correlates well with protein levels, in general. As Dr. Polakis explains, the primary focus of the microarray project was to identify tumor cell markers useful as targets for both the diagnosis and treatment of cancer in humans. The scientists working on the project extensively rely on results of microarray experiments in their effort to identify such markers. As Dr. Polakis explains, using microarray analysis, Genentech scientists have identified approximately 200 gene transcripts (mRNAs) that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To the date of the Declaration, they have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Having compared the levels of mRNA and protein in both the tumor and normal cells analyzed, they found a very good correlation between mRNA and corresponding protein levels. Specifically, in approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA. While the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested according to the Polakis Declaration greatly exceeds this legal standard. Based on these experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states that, for human genes, increased mRNA levels typically correlate with an increase in abundance of the encoded protein. He further confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

Appellants further note that the sale of gene expression chips to measure mRNA levels is a highly successful business, with a company such as Affymetrix recording 168.3 million dollars in sales of their GeneChip® arrays in 2004. Clearly, the resear ch community believe that the

information obtained from these chips is useful (i.e., that it is more likely than not that the results are informative of protein levels).

Therefore, in the majority of amplified genes, the teachings in the art, overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels.

In the Final Office Action (page 8) mailed September 16, 2004, the Examiner alleges regarding Ornoft *et al.*, Hyman *et al.* and Pollack *et al.* that:

> "Ornoft *et al.* do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time....Ornoft *et al.* concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (p.40). This analysis was not done for PRO341 in the instant specification. That is, it is not clear whether or not PRO341 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, the relevance, if any of Ornoft *et al.* is not clear."
>
> "Hyman *et al.* used the same CGH approach in their research. Less than half (44%) of highly amplified genes showed mRNA overexpression (abstract).... Therefore, Hyman *et al.* also do not support utility of the polypeptides of the instant invention."
>
> "Pollack *et al.*, also used CGH technology, concentrating on large chromosome regions showing high amplification (p. 12965). Pollack *et al.* did not investigate polypeptide levels.... Therefore, Pollack *et al.* also do not support the asserted utility of the claimed invention."

Appellants respectfully point out that in Ornoft *et al.*, 1,800 genes that yielded an increase or decrease in mRNA expression in two invasive tumors compared to the two non-invasive papillomas were then mapped to chromosomal locations. The chromosomes had already been analyzed for amplification by hybridizing tumor DNA to normal metaphase chromosomes (CGH). Ornoft *et al.* used CGH alterations as the independent variable and estimated the frequency of expression alterations of the 1,800 genes in the chromosomal areas. Ornoft *et al* found that in general (77% and 80% concordance) areas with a strong gain of chromosomal material contained a cluster of genes having increased mRNA expression (see page 40). Ornoft *et al.* state, "For both tumors TCC733 ($p<0.015$) and TCC827 ($p<0.00003$) a highly significant correlation was observed between the level of CGH ratio change (reflecting the DNA copy number) and alterations detected by the array based technology" (see page 41, column 1). Ornoft *et al.*, also studied the relation between altered mRNA and protein levels using 2D-

PAGE analysis. Orntoft *et al.* state, "In general there was a highly significant correlation ($p<0.005$) between mRNA and protein alterations.... 26 well focused proteins whose genes had a known chromosomal location were detected in TCCs 733 and 335, and of these 19 correlated ($p<0.005$) with the mRNA changes detected using the arrays." (See page 42, column 2 to page 34, column 2). Accordingly, Orntoft *et al.* clearly support Appellants' position that proteins expressed by genes that are amplified in tumors are useful as cancer markers. The Examiner has stated that Appellants have not indicated whether PRO341 is in a gene cluster region of a chromosome. Appellants fail to see how this is relevant to the analysis. Orntoft *et al.* did not limit their findings to only those regions of amplified gene clusters.

Appellants respectfully submit that the Examiner has mischaracterized the methods used by Hyman *et al.* and Pollack *et al* in their analysis. These papers did not use traditional CGH analysis to identify amplified genes. Hyman *et al.* and Pollack *et al.* did gene-by-gene analysis across all chromosomes. In Hyman *et al.*, 13,824 cDNA clones were placed on glass slides in a microarray and genomic DNA from breast cancer cell lines and normal human WBCs was hybridized to the cDNA sequences. For expression analysis, RNA from tumor cell lines was hybridized on the same microarrays. The 13,824 arrayed cDNA clones were analyzed for gene expression and gene copy number in 14 breast cancer cell lines. Hyman *et al.* state, "The results illustrate a considerable influence of copy number on gene expression patterns." For example, Hyman *et al.* teach that "[u]p to 44% of the highly amplified transcripts (CGH ratio, >2.5) were overexpressed (*i.e.*, belonged to the global upper 7% of expression ratios) compared with only 6% for genes with normal copy number." (See page 6242, column 1). Further, Hyman *et al.* state that "[t]he cDNA/CGH microarray technique enables the direct correlation of copy number and expression data on a gene-by-gene basis throughout the genome." (See page 6242, column 2). Therefore, the analysis performed by Hyman *et al.* was on a gene-by gene basis, and clearly shows that "it is more likely than not" that a gene which is amplified in tumor cells will have increased gene expression.

In Pollack *et al.*, DNA copy number alteration across 6,691 mapped human genes in 44 predominantly advanced primary breast tumors and 10 breast cancer cell lines was profiled. Pollack *et al.* further state, "Parallel microarray measurements of mRNA levels reveal the remarkable degree to which variation in gene copy number contributes to variation in gene expression in tumor cells." (See Abstract). "Genome-wide, of 117 high-level DNA

amplifications (fluorescence ratios >4, and representing 91 different genes), 62% (representing 54 different genes; ...) are found associated with at least moderately elevated mRNA levels (mean-centered fluorescence ratios >2), and 42% (representing 36 different genes) are found associated with comparably highly elevated mRNA levels (mean-centered fluorescence ratios >4)." (See page 12966, column 1). Therefore, the analysis performed by Pollack *et al.* was also done on a gene-by gene basis, and clearly shows that "it is more likely than not" that a gene which is amplified in tumor cells will have increased gene expression.

With regard to the correlation between mRNA expression and protein levels, the Examiner has asserted that the Polakis Declaration is insufficient to overcome the rejection of pending claims 124-126 and 129-131 since:

> "the instant specification provides no information regarding mRNA levels of PRO341....only gene amplification data was presented.....the declaration does not provide data such that the Examiner can independently draw conclusions." (Page 9 of the Final Action).

Appellants respectfully submit that Dr. Polakis' Declaration was presented to support the position that there is a correlation between mRNA levels and polypeptide levels, the correlation between gene amplification and mRNA levels having already been established by the data shown in the Orntoft *et al.,* Hyman *et al.,* and Pollack *et al.* articles. Appellants further emphasize that the opinions expressed in the Polakis Declaration, including in the above quoted statement, are all based on factual findings. Regarding the non-acceptance of the Polakis declaration by the Examiner, Appellants draw the Examiner's attention to case law that clearly establishes that in considering affidavit evidence, the Examiner must consider all of the evidence of record anew (*In re Rinehart,* 531 F.2d 1084, 189 USPQ 143 (C.C.P.A. 1976) and *In re Piasecki,* 745 F.2d. 1015, 226 USPQ 881 (Fed. Cir. 1985)). "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument" (*In re Alton,* 37 USPQ2d 1578 (Fed. Cir 1966) at 1584 quoting *In re Oetiker,* 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992)). Furthermore, the Federal Court of Appeals held in *In re Alton*, "We are aware of no reason why opinion evidence relating to a fact issue should not be considered by an examiner" (*In re Alton, supra.*). Appellants further draw the Examiner's

attention to the Utility Examination Guidelines (Part IIB, 66 Fed. Reg. 1098 (2001)) which states,

> "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered."

The statement in question from the Polakis Declaration that "it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell" is based on his own experimental findings, which is clearly set forth in the Declaration. Accordingly, the fact-based conclusions of Dr. Polakis would be considered reasonable and accurate by one skilled in the art.

The Examiner further cites the Hu *et al.* reference and concludes that:

> "the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue.....Hu *et al.* discovered that genes displaying a 5-fold change or less (mRNA expression) in tumors compared to normal showed no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section)" (emphasis added).

Appellants respectfully submit that, contrary to the Examiner's assertion, the Hu *et al.* reference does not conclusively establish a *prima facie* case for lack of utility for the PRO341 molecule, for the reasons outlined below.

The Hu *et al.* reference is entitled "Analysis of Genomic and Proteomic Data using Advanced Literature Mining" (emphasis added). Therefore, as the title itself suggests, the conclusions in this reference are based upon statistical analysis of information obtained from published literature, and not from experimental data. Hu *et al.* performed statistical analysis to provide evidence for a relationship between mRNA expression and biological function of a given molecule (as in disease). The conclusions of Hu *et al.* however, only apply to a specific type of breast tumor (estrogen receptor (ER)-positive breast tumor) and cannot be generalized to breast cancer genes in general, let alone to cancer genes in general. Interestingly, the observed

correlation was only found among ER-positive (breast) tumors not ER-negative tumors." (See page 412, left column).

Moreover, the analytical methods utilized by Hu *et al.* have certain statistical drawbacks, as the authors themselves admit. For instance, according to Hu *et al.*, "*different* statistical methods" were applied to "*estimate* the strength of gene-disease relationships and evaluated the results." (See page 406, left column, emphasis added). Using these different statistical methods, Hu *et al.* "[a]ssessed the relative strengths of gene-disease relationships based on the frequency of both co-citation and single citation." (See page 411, left column). As is well known in the art, different statistical methods allow different variables to be manipulated to affect the resulting outcome. In this regard, the authors disclose that, "Initial attempts to search the literature" using the list of genes, gene names, gene symbols, and frequently used synonyms generated by the authors "revealed several sources of false positives and false negatives." (See page 406, right column). The authors add that the false positives caused by "duplicative and unrelated meanings for the term" were "difficult to manage." Therefore, in order to minimize such false positives, Hu *et al.* disclose that these terms "had to be eliminated entirely, thereby reducing the false positive rate but unavoidably under-representing some genes." *Id.* (emphasis added). Hence, Hu *et al.* had to manipulate certain aspects of the input data, in order to generate, in their opinion, meaningful results. Further, because the frequency of citation for a given molecule and its relationship to disease only reflects the current research interest of a molecule, and not the true biological function of the molecule, as the authors themselves acknowledge, the "[r]elationship established by frequency of co-citation do not necessarily represent a true biological link." (See page 411, right column). Therefore, based on these findings, the authors add, "[t]his may reflect a bias in the literature to study the more prevalent type of tumor in the population. Furthermore, this emphasizes that caution must be taken when interpreting experiments that may contain subpopulations that behave very differently." *Id.* (Emphasis added). In other words, some molecules may have been underrepresented merely because they were less frequently cited or studied in literature compared to other more well-cited or studied genes. Therefore, Hu *et al.*'s conclusions do not represent genes in general.

Therefore, Applicants submit that, based on the nature of the statistical analysis performed herein, and in particular, based on Hu's analysis of one class of genes, namely, the estrogen receptor (ER)-positive breast tumor genes, the conclusions drawn by the Examiner,

namely that, "genes displaying a 5-fold change or less (mRNA expression) in tumors compared to normal showed no evidence of a correlation between altered gene expression and a known role in the disease (in general)" is not reliably supported.

Therefore summarizing the conclusions drawn from the references cited so far, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is a correlation between polypeptide and mRNA levels, these instances are exceptions rather than the rule. In the majority of amplified genes, the teachings in the art, as exemplified by Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, the Polakis Declaration, etc. overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. The references cited by the Examiner, namely, Pennica *et al.* and Konopka *et al.*, Hu *et al.*, are not sufficient to establish a *prima facie* case of lack of utility since they do not teach anything whatsoever about the correlation of protein expression and gene amplification for genes in general. In fact, one of the Examiner's cited reference, Haynes *et al.* supports the Appellants position that gene amplification mostly correlates well with protein expression because **most** of the 80 diverse, yeast genes studied in Haynes showed some positive correlation (see Figure 1 of Haynes *et al.*). To establish a *prima facie* case of lack of utility, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility made by the Appellant. Such a showing has clearly not been done. Therefore, one of skill in the art would reasonably expect, based on the amplification data for the PRO341 gene, that the PRO341 polypeptide is also concomitantly overexpressed.

Appellants submit that even assuming *arguendo* that a *prima facie* case of lack of utility (that it is more likely than not that there is no correlation between gene amplification and increased mRNA/protein expression) were established, which Appellants submit is **not** true, a polypeptide encoded by a gene that is amplified in cancer would **still** have a specific, substantial, and credible utility. In support, Appellants respectfully draw the Board's attention to page 2 of the Declaration of Dr. Avi Ashkenazi (submitted with the Response filed October 24, 2003) which explains that,

> even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment.

Thus, even if over-expression of the gene product does not parallel gene amplification in certain tumor types, parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified in a tumor, but the corresponding gene product is not over-expressed, the clinician will decide not to treat a patient with agents that target that gene product. This not only saves money, but also has the benefit that the patient can avoid exposure to the side effects associated with such agents.

This utility is further supported by the teachings of the article by Hanna and Mornin. (Pathology Associates Medical Laboratories, August (1999), submitted with the Response filed July 7, 2004). The article teaches that the HER-2/neu gene has been shown to be amplified and/or over-expressed in 10%-30% of invasive breast cancers and in 40%-60% of intraductal breast carcinomas. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the over-expression of the HER-2/neu gene product (by IHC). Even when the protein is not over-expressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

The Examiner asserts that,

> "Hanna *et al.* supports the rejection, in that Hanna *et al.* show that gene amplification does not reliably correlate with polypeptide overexpression, and thus the level of polypeptide expression must be tested empirically." (Page 11 of the Final Office Action mailed September 16, 2004).

Appellants respectfully point out that the Examiner appears to have misread Hanna *et al.* Hanna *et al.* clearly state that gene amplification (as measured by FISH) and polypeptide expression (as measured by immunohistochemistry, IHC) are well correlated ("in general, FISH and IHC results correlate well" (Hanna *et al.* p. 1, col. 2)). It is only a subset of tumors which show discordant results. Thus, Hanna *et al.* support Appellants' position rather well that it is more likely than not that gene amplification correlates with increased polypeptide expression. Further, the purpose of using IHC as a screen is not, as stated by the Examiner, to "test empirically" polypeptide expression. Rather, the authors make clear that the screening strategy is "based upon the above considerations," that is, for the selection of patients who should receive treatment with

Herceptin, as discussed in the immediately preceding paragraph. Thus the purpose of measuring both protein and gene levels is not for further experimentation, but rather, for further characterization of the tumors into medically relevant categories.

Appellants have clearly shown that the gene encoding the PRO341 polypeptide is amplified in at least 3 primary lung carcinoma tumors. Therefore, the PRO341 gene, similar to the HER-2/neu gene disclosed in Hanna *et al.*, is a tumor associated gene. Furthermore, as discussed above, in the majority of amplified genes, the teachings in the art overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO341 gene, that the PRO341 polypeptide is concomitantly overexpressed and is useful in tumor categorization. Therefore, this rejection should be withdrawn based on consideration of the totality of evidence.

As a final note, Appellants submit that the utility presently asserted for the claimed invention meets the "substantiality" requirement set forth by the Utility Guidelines and required by the U.S. Supreme Court in Brenner v. Manson, 383 U.S. 519 (1966).

Hence, it is respectfully requested that that the outstanding rejection to Claims 124-126 and 129-131 be reconsidered and that the rejection be reversed.

2. Claims 124-126 and 129-131 also stand rejected under 35 U.S.C. §112, first paragraph since allegedly "the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well-established utility, one skilled in the art clearly would not know how to use the claimed invention."

Appellants respectfully traverse the rejection.

On page 4 and 5, line 2 of the Final Office Action mailed on September 16, 2004, the Examiner adds:

> "The asserted utility is not substantial.....Therefore, further research would be required by the skilled artisan to determine if the disclosed results regarding a gene amplification event in tumors is also reflected at the mRNA and polypeptide levels....." (emphasis added).

In this regard, Appellants refer to the arguments and information presented above, particularly to the sections referring to the Ashkenazi Declaration and the Hanna and Mornin reference, in

response to the outstanding rejection under 35 U.S.C. §101, wherein those arguments are incorporated by reference herein. As explained therein, even if gene amplification were not to result in overexpression of the gene product (*i.e.*, the protein), an analysis of the expression of the protein is useful in determining the course of treatment, as supported by the Ashkenazi Declaration. The Examiner appears to view such testing described in the Ashkenazi Declaration and the Hanna paper as experiments involving further characterization of the PRO341 polypeptide itself. On the contrary, such testing is for the purpose of characterizing not the PRO341 polypeptide, but the tumors in which the gene encoding PRO341 is amplified. That is, such further testing or research is for the purpose of characterizing the tumors into medically relevant categories in which the gene encoding PRO341 is/ is not amplified, and such techniques were routine in the art of clinical oncology at the time of filing of the instant application, as evidenced by the teaching of Hanna and Mornin.

Thus, based on the asserted utility for PRO341 in the diagnosis of selected lung carcinomas, the reduction to practice of the instantly claimed protein sequence of SEQ ID NO: 20 in the present application (also see page 305), the disclosure of the step-by-step protocols for making chimeric PRO polypeptides, including those wherein the heterologous polypeptide is an epitope tag or an Fc region of an immunoglobulin in the specification (at page 374, lines 24 to page 375, line 9), the disclosure of a step-by-step protocol for making and expressing PRO341 in appropriate host cells (in Examples 140-143 and page 376, line 12), the step-by-step protocol for the preparation, isolation and detection of monoclonal, polyclonal and other types of antibodies against the PRO341 protein in the specification (at pages 390-395) and the disclosure of the gene amplification assay in Example 170, the skilled artisan would know exactly how to make and use the claimed polypeptide for the diagnosis of lung carcinoma. Appellants submit that based on the detailed information presented in the specification and the advanced state of the art in oncology, the skilled artisan would have found such testing routine and not 'undue'.

Therefore, since the instantly claimed invention is supported by either a credible, specific and substantial asserted utility or a well-established utility, and since the present specification clearly teaches one skilled in the art "how to make and use" the claimed invention without undue experimentation, Appellants respectfully request reconsideration and reversal of this outstanding rejection to Claims 124-126 and 129-131.

## VIII. CONCLUSION

For the reasons given above, Appellants submit that present specification clearly describes, details and provides a patentable utility for the claimed invention. Moreover, it is respectfully submitted that based upon this disclosed patentable utility, the present specification clearly teaches "how to use" the presently claimed polypeptide. As such, Appellants respectfully request reconsideration and reversal of the outstanding rejection of claims 124-126 and 129-131.

Respectfully submitted,

Date: July 26, 2005

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## APPENDIX A

## Claims on Appeal

124. An isolated polypeptide comprising:

(a) the amino acid sequence of the polypeptide of SEQ ID NO: 20;

(b) the amino acid sequence of the polypeptide of SEQ ID NO: 20, lacking its associated signal peptide;

(c) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209792;

wherein, the nucleic acid encoding said polypeptide is amplified in lung cell carcinomas.

125. The isolated polypeptide of Claim 124 comprising the amino acid sequence of the polypeptide of SEQ ID NO:20.

126. The isolated polypeptide of Claim 124 comprising the amino acid sequence of the polypeptide of SEQ ID NO:20, lacking its associated signal peptide.

129. The isolated polypeptide of Claim 124 comprising the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209792.

130. A chimeric polypeptide comprising a polypeptide according to Claim 124 fused to a heterologous polypeptide.

131. The chimeric polypeptide of Claim 130, wherein said heterologous polypeptide is an epitope tag or an Fc region of an immunoglobulin.